MALIGNANT LYMPHOMAS

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(Updated August 2010)

Malignant lymphomas consist of Hodgkin and non-Hodgkin lymphomas. The current management of these diseases involves a multi-disciplinary approach. An excisional biopsy of the involved lymph node is necessary to make an accurate diagnosis of the histological sub type of the lymphoma, with definitive treatment consisting of chemotherapy or combined treatment with chemotherapy and radiation.

- Lymphomas primarily involve lymph nodes, with cervical nodes being the most commonly involved. Extranodal organs like thyroid, bone, GI tract, CNS, can be the primary site of disease in one-third of cases in non-Hodgkin's lymphoma, but are rarely involved in Hodgkin's lymphoma.

- Lymphomas may be associated with B-symptoms of fever > 38^{o}C, drenching night sweats and weight loss of >10% over 6 months.

I. CLASSIFICATION

1. Hodgkin Lymphoma (HL)

- Classification for HL is the World Health Organization (WHO) system (see table)
- The cell of origin in HL is a B-cell
- Association between HL and Epstein-Barr Virus (EBV)

WHO Classification	
Nodular Lymphocyte Predominant HL(NLPHL) (5%) (CD15-, CD30-)	best prognosis ↓
Classic HL (95%) (CD15+, CD30+)	worse prognosis
- lymphocyte rich (LR) - nodular sclerosis (NS) - mixed cellularity (MC) - lymphocyte depleted (LD)	

2. Non-Hodgkin Lymphoma (NHL)

- NHL's are a heterogenous group of diseases that represent a clonal expansion of lymphoid cells

- A histological classification called the ***Working Formulation*** was, until recently, primarily used for classifying non-Hodgkin's lymphomas. It is based on the H&E morphology and clinical outcome, and divides non-Hodgkin's lymphomas into low, intermediate and high grade categories.

- More recently, increasing knowledge about the immune system and genetic abnormalities has lead to the *Revised European American Lymphoma* **(REAL***) system*. A modified REAL system is now called the World Health Organisation (**WHO**) classification, and separates B-cell malignancies from T- and NK-cell malignancies, and also divides lymphomas into immature precursor cells and mature (or peripheral) cells (see appendix 1).

- Most common subtypes are diffuse large B-cell (30%) and follicular lymphoma (20%)

Table 1: Working Formulation for NHL

Classification	Medium Survival
Low grade – indolent	5-10 years
Intermediate grade – aggressive	2-5 years
High grade - very aggressive	0.5-2 years

II. STAGING

1. Staging Investigations

- History and physical exam including all nodes, liver, spleen
- Excisional biopsy of palpable nodes
- Complete blood count and a differential white blood count
- Liver and kidney function tests
- ESR, LDH which is a marker of tumor burden
- Chest x-ray
- CT scans of chest, abdomen and pelvis
- Bone marrow biopsy (only in advanced stage disease in HL)
- Gallium scan (useful with bulky disease) to follow response to treatment
- PET scan (instead of a Gallium scan if available), more sensitive and specific than Gallium scan

2. Staging System

- Same system is used for staging both Hodgkin lymphoma and non-Hodgkin lymphoma
- This is the modified Ann Arbor (Cotswolds) staging system
- Based on biopsy and clinical staging studies

Table 2: Ann Arbor Staging

Stage I	• Single nodal region (I) • Single extra-nodal site (IE)
Stage II	• Two or more node regions on same side of diaphragm (II)
Stage III	• Node regions on both sides of diaphragm (III) • Spleen involvement (IIIs)
Stage IV	• Involvement of extralymphatic organ(s) + regional nodes (Iv)
All stages divided into A or B	• Without weight loss/fever/night sweats (eg IA) • With weight loss/fever/night sweats (eg IB)
B symptoms = **fever > 38°C, night sweats and/or weight loss ≥ 10% of body weight in preceding 6 months*	

X – designates bulky disease (ie mass ≥ 10cm) in Cotswolds system

III. PROGNOSTIC FACTORS

I. **HL**

- stage is most important factor and determines treatment

1. Stage of the disease
2. Age (>50)
3. Histological type
4. Presence of B-symptoms
5. Disease bulk, (nodal size or mediastinal mass >10cms)
6. Elevated ESR and LDH
7. Performance status (Karnofsky performance Scale - see appendix2)

II. **NHL**

An **"International Prognostic Index"** was developed taking some of the above factors into consideration for NHL

1. **Adverse prognostic factors in follicular lymphoma**
   - based on Follicular Lymphoma International Prognostic Index (FLIPI)

   - Age >60 yrs
   - Elevated LDH
   - Stage III or IV
   - Number of nodal areas >4
   - Hemoplobin <120gIL

2. **Adverse prognostic factors in Diffuse large B-cell lymphoma**
- based on the International Prognostic Index (IPI)

IPI Index

- Age >60 yrs
- Poor performance status (ECOG 2-4)
- Elevated LDH
- Stage III or IV
- Extranodal disease involving >1 site

- with use of CHOP-R, this is now the

Revised IPI Score

	Number of Factors	4-yr survival (%)
Very good	0	92%
Good	1-2	82%
Poor	3-5	58%

IV. TREATMENT

1. Hodgkin Lymphoma (HL)

i) **Nodular Lymphocyte-Predominant HL**:

- most present with early stage disease
- treated with involved-field radiation (IFRT) i.e. radiation to involved nodal region only
- chemotherapy not indicated in early stage disease
- 10 year survival = 90%

ii) **Classic HL**

Early stage, good prognostic features (Stage I-IIA)

- ABVD chemotherapy x 2 cycles + IFRT
- ABVD = adriamycin, bleomycin, vinblastine, dacarbazine

Advanced stage, poor prognostic features (Stage IB-IV)

- ABVD x 6-8 cycles
- radiotherapy (RT) to areas of bulky disease or to areas of partial response after chemo

Recurrent/Resistant HL

- high dose chemotherapy and stem cell transplant $\pm$ RT

Prognosis of Classic Hodgkin's Disease

Stages I and IIA – 5 year relapse-free survival is > 90%
Stages IIB and IIIA – 5 year relapse-free survival between 75-85%
Stages IIIB and IV – 5 year relapse-free survival is 30 to 50%

2. Non-Hodgkin's Lymphoma (NHL)

i) **Low Grade**:

- Represent 30-40% of all lymphomas and most present as advanced stage disease.
- Follicular lymphoma is most common.
- Clinical course is indolent.
- Spontaneous remissions and transformation into intermediate or high grade lymphoma can occur.

Limited stage (Stage I and IIA)

- Treatment with involved field radiation can result in long-term disease free survival and potential cure.

Advanced Stage Disease (Stages III and IV)

- Early treatment does not alter overall survival. Therefore, asymptomatic patients are closely followed with no active treatment.

- Treatment is offered for progressive adenopathy, organ compromise, bone marrow failure or constitutional symptoms.

- Standard first-line treatment is now combination chemo with **CVP-R** (Cyclophosphamide, Vincristine, Prednisone, Rituximab)

ii) **Intermediate Grade**

- 50% of these patients are potentially curable.
- Most common is large B-cell lymphoma.

Limited stage (Stage I and IIA, non-bulky disease <10cms.)

- Treatment is with combination chemo and ritaxumab (a CD-20 targeted therapy) and radiation. **CHOP-R** x 3 cycles followed by involved-field radiation (IFRT).

- CHOP-R = Cyclophosphamide, Adriamycin, Vincristine, Prednisone, Rituximab

Advanced Stage (Stage III and IV, bulky disease, B-symptoms)

- Standard of care is Anthracycline based chemotherapy (CHOP to complete remission + 2 extra cycles for a maximum of 8 cycles).

- Adjuvant radiation to sites of bulky disease or partial response

Refractory or relapsed disease

- High dose chemotherapy followed by stem cell transplant.

iii) **High Grade**

- eg. Burkitt's Lymphoma
- grow quickly and require urgent and aggressive chemotherapy
- treated similar to acute lymphoblastic leukemia (ALL)

Appendix I: WHO Classification of Non-Hodgkin's Lymphoma

B-CELL LYMPHOMAS	T-/NK-CELL LYMPHOMAS
Precursor B-Cell	**Precursor T-Cell**
• B Lymphoblastic	• T Lymphoblastic
Mature (Peripheral) B-Cell	**Mature (Peripheral) T-Cell**
• Diffuse large B-cell lymphoma*	• Peripheral T-cell lymphoma
• Follicular lymphoma*	**Not otherwise specified**
• Small lymphocytic lymphoma (CCL)	**Angioimmunoblastic T-cell lymphoma**
	Extranodal nasal NK/T-cell lymphoma
• Extranodal marginal zone B-cell lymphomas of MALT type*	Enteropathy-type T-cell lymphoma
• Nodal Marginal zone B-cell lymphoma	Hepatosplenic gamma-delta T-cell lymphoma
• Splenic marginal zone B-cell lymphoma	Subcutaneous panniculitis-like T-cell lymphoma
• Lymphoplasmacytic lymphoma	• Anaplastic large T-/null-cell lymphoma
• Burkitt's lymphoma	• Mycosis fungoides/Sezary syndrome • Adult T-cell lymphoma/leukemia

*Account for more than 50% of NHL cases
WHO = World Health Organization; NK = natural killer cells;
CLL = chronic lymphocytic leukemia; MALT = mucosa-associated lymphoid tissue

Appendix II: Criteria For Performance Status On The Karnofsky Performance Scale And ECOG Performance Scale

KARNOFSKY PERFORMANCE SCALE		ECOG PERFORMANCE SCALE	
100	Normal; no complaints; no evidence of disease	0	Normal activity; asymptomatic
90	Able to carry on normal activity minor signs or symptoms of disease	1	Symptomatic; fully ambulatory
80	Normal activity with effort; some signs or symptoms of disease		
70	Cares for self; unable to carry on normal activity or to do active work	2	Symptomatic; in bed < 50% of time
60	Requires occasional assistance but is able to care for most needs		
50	Requires considerable assistance and frequent medical care	3	Symptomatic, in bed > 50% of time; not bedridden
40	Disabled; requires special care and assistance		
30	Severely disabled; hospitalization is indicated although death no imminent		
20	Very sick; hospitalization necessary; active supportive treatment is necessary	4	100% bedridden
10	Moribund, fatal processes progressing rapidly		
0	Dead	5	Dead